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Have antiepileptic drug prescription claims changed following the FDA suicidality warning? An evaluation in a state Medicaid program ☆

Manish Mittal [a,*,1], Donald L. Harrison [b,2], Michael J. Miller [c,3], Kevin C. Farmer [b,4], David M. Thompson [d,5], Yu-Tze Ng [e,6]

[a] Health Economics and Outcomes Research, AbbVie, North Chicago, IL, USA
[b] Department of Pharmacy, Clinical and Administrative Sciences, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[c] Department of Pharmacy, Clinical and Administrative Sciences, The University of Oklahoma Health Sciences Center, Tulsa, OK, USA
[d] Department of Biostatistics and Epidemiology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[e] Department of Neurology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

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ABSTRACT

Objective: In January 2008, the Food and Drug Administration (FDA) communicated concerns and, in May 2009, issued a warning about an increased risk of suicidality for all antiepileptic drugs (AEDs). This research evaluated the association between the FDA suicidality communications and the AED prescription claims among members with epilepsy and/or psychiatric disorder.

Methods: A longitudinal interrupted time-series design was utilized to evaluate Oklahoma Medicaid claims data from January 2006 through December 2009. The study included 9289 continuously eligible members with prevalent diagnoses of epilepsy and/or psychiatric disorder and at least one AED prescription claim. Trends, expressed as monthly changes in the log odds of AED prescription claims, were compared across three time periods: before (January 2006 to January 2008), during (February 2008 to May 2009), and after (June 2009 to December 2009) the FDA warning.

Results: Before the FDA warning period, a significant upward trend of AED prescription claims of 0.01% per month (99% CI: 0.008% to 0.013%, $p < 0.0001$) was estimated. In comparison to the prewarning period, no significant change in trend was detected during (−20.0%, 99% CI: −70.0% to 30.0%, $p = 0.34$) or after (80.0%, 99% CI: −20.0% to 200.0%, $p = 0.03$) the FDA warning period. After stratification, no diagnostic group (i.e., epilepsy alone, epilepsy and comorbid psychiatric disorder, and psychiatric disorder alone) experienced a significant change in trend during the entire study period ($p > 0.01$).

Conclusions: During the time period considered, the FDA AED-related suicidality warning does not appear to have significantly affected prescription claims of AED medications for the study population.

1. Introduction

In January 2008, the FDA issued an alert, which was followed later (May 2009) with a warning concerning an increased risk of suicidality, defined as suicidal ideation and behavior for all antiepileptic drugs (AEDs) [1]. Both the alert and the warning were based on the analysis of data from 199 clinical trials involving 43,892 patients that demonstrated that patients taking AEDs (0.43%) had approximately twice the risk of suicidality (RR = 1.82, 95% CI: 1.25 to 2.68) compared to patients taking placebo (0.24%) [2].

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* Corresponding author at: Department GMH1, AP31-1 NE, 1 North Waukegan Road, North Chicago, IL 60064, USA. Tel.: +1 847 935 9190 (office), +1 917 379 3390 (mobile); fax: +1 847 937 1992.

E-mail addresses: manish.mittal@abbvie.com (M. Mittal), donald-harrison@ouhsc.edu (D.L. Harrison), michael-miller@ouhsc.edu (M.J. Miller), kevin-farmer@ouhsc.edu (K.C. Farmer), dave-thompson@ouhsc.edu (D.M. Thompson), Y-Ng@ouhsc.edu (Y.-T. Ng).

[1] I, 'Manish Mittal', am currently an employee of Abbvie. However, during the conduct of this research I was a doctoral student at the OUHSC. Abbvie is in no manner associated with this research.

[2] 1110 N Stonewall, College of Pharmacy, CPB 239, P.O. Box 26901, Oklahoma City, OK 73190-5040, USA. Tel.: +1 405 271 6878x47247; fax: +1 405 271 6430.

[3] 4502 East 41st Street, College of Pharmacy, 2H36, Tulsa, OK 74135, USA. Tel.: +1 918 660 3586; fax: +1 918 660 3009.

[4] 1110 N Stonewall, College of Pharmacy, CPB 245, P.O. Box 26901, Oklahoma City, OK 73190-5040, USA. Tel.: +1 405 271 6878x47825; fax: +1 405 271 6430.

[5] 801 Northeast 13th Street, Room 352, P.O. Box 26901, Oklahoma City, OK 73126-0901, USA. Tel.: +1 405 271 2229x48054.

[6] 920 Stanton L. Young Blvd Ste 2040, Oklahoma City, OK 73104, USA. Tel.: +1 405 271 8000 push 1 then x46046; fax: +1 405 271 5723.

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The FDA analysis was received with great skepticism by many clinicians, as well as by several professional organizations, specifically the American Epilepsy Society (AES) [3]. Some independent investigators questioned the validity of the FDA findings after identifying serious methodological flaws [4,5]. Since the release of the warning, a number of observational studies have investigated the association between AEDs and suicidality [6–11]. These results have been conflicting with some studies reporting an increased risk of suicidality [6–9] while others reporting no increased risk [10,11].

The FDA communication and conflicting evidence available may complicate the decision to prescribe AEDs. Shneker et al. [12] surveyed 175 neurologists, and 46% of practitioners reported no change in clinical practice because of the FDA alert. However, the study response rate was only 22%, and the results may not be representative of all neurologists and/or prescribers of AEDs.

This study further attempts to quantify and evaluate the association between dissemination of the FDA suicidality warning and AED prescription claims among Oklahoma Medicaid members diagnosed with epilepsy and/or psychiatric disorder(s) from January 2006 through December 2009.

2. Material and methods

2.1. Study design

A longitudinal interrupted time-series analysis of Oklahoma Medicaid claims data from January 2006 through December 2009 was used to evaluate the change in AED prescription claims before and after the FDA suicidality alert and warning. A time series of 48 consecutive months was created using person-month level data as a unit of analysis. For each month, the proportion of members with an AED prescription claim was calculated.

Two interruptions were introduced during the study period. The first interruption was the month (January 2008) when the FDA alert was issued. The second interruption was the month (May 2009) when the FDA warning was issued. These two interruptions created 3 time segments with 2 change points in a time series of 48 months. The Medicaid administrative data comprised the analytical file for a time series of variables with aggregated values spanning 25 months before, 16 months during, and 7 months after the FDA warning. This study was reviewed and approved by the IRB at the University of Oklahoma.

2.2. Study population

A historical cohort was selected from the Oklahoma Medicaid administrative claims data which include eligibility, medical, and pharmacy claims files. All three files included data elements to identify unique members to permit matching records across the files.

Fig. 1 depicts the member inclusion and exclusion process. There were 1,183,668 members enrolled in the Oklahoma Medicaid program between January 2006 and December 2009. A group of 14,881 continuously eligible members was selected who were less than 65 years of age, were not dually-eligible for Medicaid and Medicare, had at least one medical claim with a diagnosis of epilepsy and/or psychiatric disorder(s) in an inpatient or outpatient setting, and had at least one AED prescription claim between January 2006 and December 2009 (Table 1).

The date of the first AED prescription claim during the study period was considered the AED prescription index date. Lacosamide (October 2008) and rufinamide (November 2008) were new branded drugs launched during the study period and excluded from the study since they involved only 29 individuals. Members were excluded if they had received a diagnosis of attempted suicide (ICD-9-CM: E950–E959) on or six months prior to the AED prescription index date or received polytherapy (2 or more AED drugs, more severely ill group) within the time period of when the days' supply of first AED claim had not been exhausted. Members with less than 15 days of AED therapy during the entire study period were also excluded, leaving the study population of 12,841 members.

After potential study members were identified, the period between July 1, 2005 and December 31, 2005 served as a prescreening period to identify prevalent (existing) members of epilepsy and/or psychiatric disorder with a diagnosis on or prior to the beginning of the study, January 2006. Subsequently, only 9289 members with existing diagnoses of epilepsy and/or psychiatric disorder were selected for the

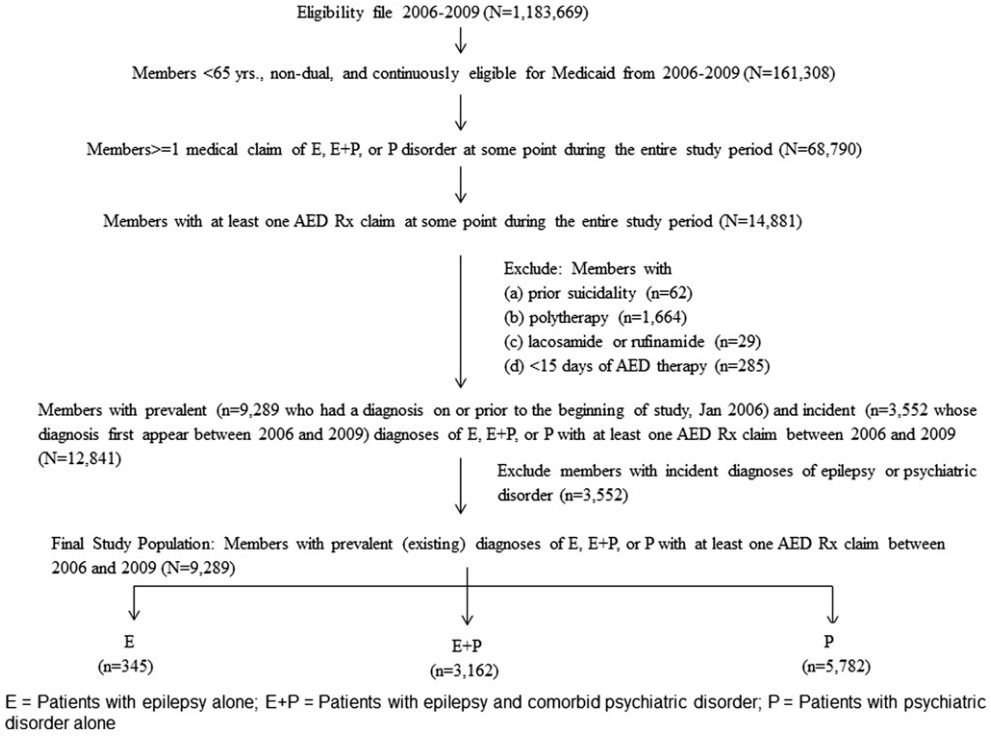

Fig. 1. Inclusion and exclusion criteria for the study population.

Table 1
A list of diagnostic groups as indicated by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and a list of antiepileptic drugs (AEDs) included in the study.

Factors	Categories (ICD-9)
I. Diagnoses	
(a) Epilepsy alone [16]	Epilepsy (345.xx) Convulsion (780.3x)
(b) Psychiatric disorder alone	Psychiatry disorder (295–319) – Depression (296.2x, 296.3x, 300.4, 311) – Bipolar disorder (296.0x, 296.1x, 296.4x–296.8x) – Schizophrenia (295.xx) – Anxiety/phobia disorder (300.0x, 300.2x, 300.3) – Adjustment disorder (309.xx) – ADHD (314.0x) – Other psychiatric disorder
(c) Epilepsy and comorbid psychiatric disorder	Patients diagnosed with both medical conditions
II. Antiepileptic drugs (AEDs)	Carbamazepine, clonazepam, clorazepam, divalproex sodium, valproic acid, ethosuximide, ethotoin, mephenytoin, methsuximide, phenytoin, primidone, lamotrigine, gabapentin, pregabalin, oxcarbazepine, levetiracetam, tiagabine, topiramate, vigabatrin, felbamate, zonisamide

final study population in order to ensure a standardized length of exposure time and to reduce bias related to the time-varying nature of an AED prescription fill (Fig. 1).

2.3. Study variables

2.3.1. Dependent variable

The filling of an AED prescription claim for at least 15 days at each monthly time point was calculated in the study population. For each member, a supply diary of AED was created by adding together consecutive filling of AED based on filling dates and the reported days supply [13]. The days supply of a prescription claim could vary from one to three months. The days supply information available from the pharmacy claims was utilized for calculating the proportion of days supply of AED during a given month for each study member. Additionally, a member could refill their AED medication before exhausting the previous fill, creating overlapping days supply [13]. In this case, the proportion of days supplied was calculated in the same manner and "credited" the member with finishing the previous fill [13]. For example, if a member filled an AED prescription claim for a 30-day supply on 1/1/07 and refilled the next prescription on 1/23/07, then that member was credited with 7 more days supply, and days supply of refilled claim was started over on 1/30/07. Members with at least 15 days of AED therapy were considered study members with an AED prescription claim for that month.

2.3.2. Independent variable

The study period of 48 months from January 2006 to December 2009 served as the independent variable. While this study focused primarily on the periods immediately before and after the introduction of the FDA warning, the study months were divided into 3 distinct time periods: (1) before the FDA warning (January 2006 to January 2008), (2) during the FDA warning (February 2008 to May 2009), and (3) after the FDA warning (June 2009 to December 2009) to more explicitly account for a potential lag period between the implementation of the FDA warning and the prescribing physicians' response to it.

2.3.3. Covariates

The selection of covariates was guided by the Andersen Behavioral Model for Access to Medical Care and included predisposing (i.e., individuals' propensity to use services), need (i.e., illness level), and enabling (i.e., individuals' ability to access services) factors that have been identified to potentially influence the use of health services [14]. Predisposing characteristics included age group, sex, and race. Need characteristics included diagnostic groups [15], neurological comorbidities [2,16–18], other comorbid conditions [19,20], and use of psychotropic drugs. Diagnostic groups comprised of members diagnosed with epilepsy alone, epilepsy and comorbid psychiatric disorder, and psychiatric disorder alone during the study period [15]. An indicator variable of neurological comorbidities was created from a list of four chronic conditions (i.e., neuropathic pain, migraine, movement disorder, or chronic pain) commonly treated with AEDs [2,16–18]. Other comorbid conditions were adjusted by estimating the Charlson comorbidity index indicating the severity of the disease and categorized into 0 or $\geq$1 comorbid score [19,20]. Use of psychotropic drugs indicated whether or not psychotropic therapy (i.e., antidepressant, antipsychotic, stimulants, or anxiolytic/hypnotic agents) was received on or prior to the AED prescription index date. Enabling characteristics included physician's specialty, geographical region, and metropolitan statistical area (MSA) status. Physicians' specialty indicated whether or not a physician was a central nervous system (CNS)-related health-care provider who had prescribed the first AED prescription to an individual (Table 2).

2.4. Statistical analysis

Univariate and descriptive statistics were used to profile all study covariates. Because of the binomial distribution of the outcome, a linear regression line was fit on a log odds (logit) scale. Segmented logistic regression models [21] using generalized estimation equations (GEE) were employed to estimate change in level (intercept) and trend (slope) in AED prescription claims during and after the FDA warning with the prewarning period as the referent. The model was adjusted for each of the predisposing, enabling, and need characteristics. Autocorrelation between repeated observations was detected using correlograms (i.e., residuals versus time) [22] and the Durbin–Watson test statistics [23] and subsequently adjusted by assuming a first-order autoregressive [AR (1)] covariance structure. Data management and analysis were accomplished via PC-SAS (v 9.2), with an a priori alpha set at 0.01 to determine statistical significance.

3. Results

The final study population consisted of 9289 continuously eligible members with prevalent diagnoses of epilepsy and/or psychiatric disorder who had filled an AED prescription claim between January 2006 and December 2009. Baseline predisposing, enabling, and need characteristics of the study population are presented in Table 2. The study population involved members who were largely children <18 years of age (39.5%), female (56.1%), and white (75.3%). The majority of the study members were diagnosed with psychiatric disorder(s) (62.3%), followed by members with epilepsy diagnoses and comorbid psychiatric disorder(s) (34.0%) and (3.7%) members with epilepsy alone.

In the overall study population, the percentage of study members with an AED prescription claim slowly but consistently increased, from 38.36% to 46.90%, between January 2006 and December 2009. Fig. 2 depicts the pattern of AED prescription claims for each diagnostic group throughout the study period. For the group of members with a diagnosis of epilepsy alone, the percentage of study members with an AED prescription claim declined over time from 72.17% to 58.55%. However, this pattern steadily increased in members with diagnoses of epilepsy and comorbid psychiatric disorder(s) trending upward from 53.42% to 63.47% and in members with psychiatric disorder(s) alone trending from 28.10% to 37.15%.

The association between the FDA suicidality warning and the antiepileptic drug prescription claims was quantified and reported using the prewarning period as a referent group (Table 3). Before the FDA warning period, a statistically significant upward trend (slope) of AED prescription claims of 0.01% per month (99% CI: 0.008% to 0.013%,

Table 2
Descriptive analysis: Predisposing, enabling, and need characteristics of the study population from January 2006 through December 2009 (N = 9289).

Characteristics	Study population, N = 9289 (%)
Predisposing characteristics	
Age	
<18	3671 (39.5%)
18–44	2936 (31.6%)
45–64	2682 (28.9%)
Sex	
Female	5212 (56.1%)
Male	4077 (43.9%)
Race	
White	6991 (75.3%)
Black	1209 (13.0%)
Other[a]	1089 (11.7%)
Need characteristics	
Diagnostic groups	
Epilepsy alone	345 (3.7%)
Epilepsy and comorbid psychiatric disorder	3162 (34.0%)
Psychiatric disorder alone	5782 (62.3%)
Neurological comorbidities[b] (neuropathic pain, migraine, movement disorder, or chronic pain)	
Yes	3799 (40.9%)
No	5490 (59.1%)
Other comorbidities[c] (Charlson comorbidity index)	
0	3325 (35.8%)
≥1	5964 (64.2%)
Use of psychotropic therapy (antidepressant, antipsychotic, stimulants, anxiolytic/hypnotics)	
Yes	7125 (76.7%)
No	2164 (23.3%)
Enabling characteristics	
CNS health-care provider[d]	
Yes	3026 (32.6%)
No	6263 (67.4%)
G. region	
NW	598 (6.4%)
SW	905 (9.7%)
OKC	2621 (28.2%)
Tulsa	1779 (19.2%)
NE	1574 (16.9%)
SE	1742 (18.8%)
MSA	
Urban	5156 (55.5%)
Rural	4004 (43.1%)

Age, sex, race, use of psychotropic therapy, physician specialty, geographical region, and MSA were measured at the AED prescription index date. Diagnostic groups, neurological comorbidities, and other comorbidities were measured during the entire study period. Percentage of geographic region and MSA did not add up to 100% because of missing data.

[a] Other races included Asian, Native Hawaiian/other Pacific Islander, American Indian/Alaska Native, and multiple races.

[b] Neurological comorbidities included a list of four chronic conditions commonly treated with AEDs, i.e., neuropathic pain [diabetes with neurological manifestations (250.6x), trigeminal nerve disorders (350.xx), glossopharyngeal neuralgia (352.1x), neuropathy (356.0x, 356.8x), postherpetic trigeminal neuralgia (053.12), and unspecified neuralgia, neuritis, and radiculitis (729.2x)]; migraine (346.xx); movement disorder [essential tremor (331.1x, 781.0x), restless legs syndrome (333.94)]; and chronic pain (338.2x, 729.1x) [2,16–18].

[c] Other comorbid conditions were adjusted by measuring the Charlson comorbidity index indicating the severity of the disease [19,20].

[d] Physicians' specialty indicated whether or not a physician was a central nervous system (CNS) health-care provider who had prescribed the first AED prescription to an individual. A list of CNS health-care providers included psychiatric hospital, intermediate care facility/mental health (ICF/MH) > 6 beds, intermediate care facility/mental health (ICF/MH) < 6 beds, outpatient mental health clinic, community mental health center (CMHC), psychologist, preadmission screening and resident review (PASRR) CMHC, health service provider in psychology (HSPP), mental health — department of mental health and substance abuse services (DMHSAS), mental health case management for all ages (public and private), neurological surgeon, neurologist, psychiatrist, and child psychiatrist.

$p < 0.0001$) was estimated. In comparison to the prewarning period, no immediate change in AED prescription claims was detected at the time of the FDA alert in January 2008 [change in level (y-intercept) = −6.5%, 99% CI: −11.3% to 0.3%, $p = 0.014$]. However, members with an AED prescription claim statistically significantly declined at the time of the FDA warning in May 2009 [change in level (y-intercept) = 14.5%, 99% CI: 8.1% to 22.6%, $p < 0.0001$]. No significant change in AED prescription claim was detected during [change in trend (slope) = −20.0%, 99% CI: −70.0 to 30.0%, $p = 0.34$] or after [change in trend (slope) = 80.0%, 99% CI: −20.0% to 200.0%, $p = 0.03$] the FDA warning period when compared to the preperiod.

The overall study population was further stratified into three mutually exclusive diagnostic groups (epilepsy alone, epilepsy and comorbid psychiatric disorder, and psychiatric disorder alone) to determine the potential change in AED prescription claims due to the FDA suicidality warning (Table 3). A significant immediate decline in AED prescription claims was detected among two diagnostic groups [epilepsy with comorbid psychiatric disorder(s) (change in level = 14.8%, 99% CI: 1.6% to 27.9%, $p = 0.005$) and psychiatric disorder(s) alone (change in level = 15.2%, 99% CI: 6.0% to 24.2%, $p < 0.0001$)] at the time of the FDA warning in May 2009 when compared to the prewarning period. Similar to the overall study population, no significant change in trend (slope) of AED prescription claims was detected in all three diagnostic groups during the entire study period ($p > 0.01$).

4. Discussion

Among our study members, there was a significant increase in the trend of AED prescription claims in the prewarning period. Although the FDA suicidality warning issued in May 2009 appeared to have a small, immediate impact on AED prescription claims, no significant change in trend was detected across any segment of the study period. This finding suggests that the FDA suicidality warning had partially "reset" the prescribing pattern to a lower level; however, over time and with experience, physicians may have assessed the risk to benefit of treatment with an AED or were unaware of the FDA risk communication [24,25].

According to Bell et al. [25] an online survey of the American Academy of Neurology (AAN) members showed that roughly 20% of healthcare professionals caring for patients with epilepsy were not aware of major FDA drug safety warnings including suicidality warning for antiepileptic medicines. Of those who were aware of the safety alerts, as few as 23% said that they remembered specific knowledge of the risks presented in a given alert. The current study supports the results of Bell et al. [25] by detecting no significant association between the FDA suicidality warning and the trend of AED prescription claims using Medicaid administrative data. Along with lack of awareness in healthcare professionals about the FDA risk communication, there are social and psychological factors (i.e., lack of media coverage and stigma associated with epilepsy) that may result in no change in AED prescription claims over time [26,27].

It is important to note that AEDs are prescribed for several other indications that are unrelated to epilepsy or psychiatric disorder. This study focused on the evaluation of the impact of the FDA suicidality warning on diagnoses of epilepsy and/or psychiatric disorder because the majority of Oklahoma Medicaid members (92%) receiving AED prescription claims were diagnosed with epilepsy and/or psychiatric disorder. In concordance with prior research [28,29], this study also determined that the majority (62.3%) of these members received an AED for a diagnosis of psychiatric disorder alone. This result is especially interesting since most AEDs prescribed for psychiatric conditions are prescribed without an FDA-approved indication [28].

For the epilepsy alone diagnostic group, the pattern of AED prescription claims appears to decline over time (Fig. 2). This is somewhat surprising because there is no alternative pharmacotherapy available for the treatment of epilepsy. Moreover, not treating patients with epilepsy may be more harmful than treating them with AEDs [30]. One potential reason for this unexpected pattern is that approximately 25% (85 out of 345) of members with epilepsy alone were less severely ill with a

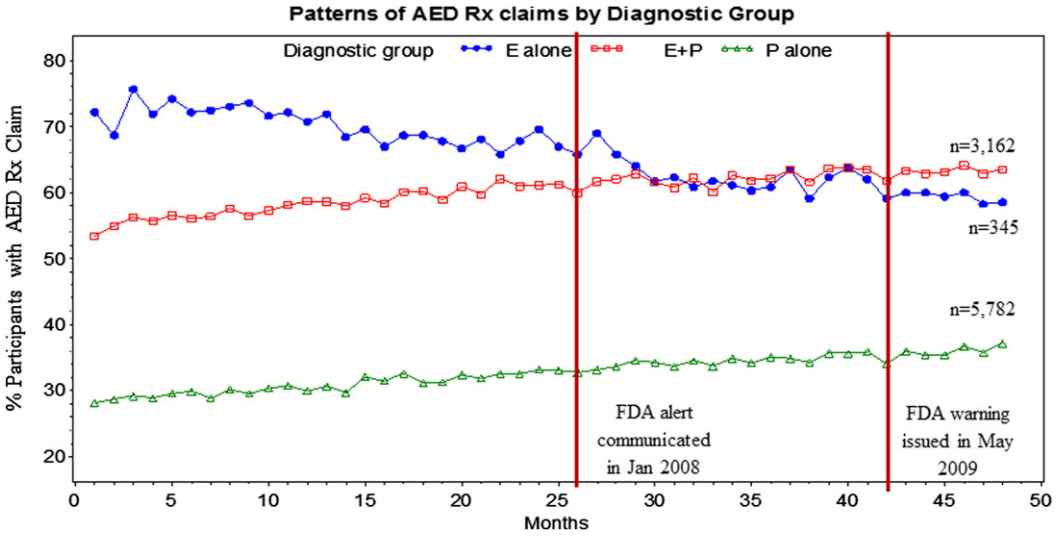

Fig. 2. Patterns of AED prescription claims in a study population diagnosed with epilepsy alone (n = 345), epilepsy and comorbid psychiatric disorder (n = 3162), or psychiatric disorder alone (n = 5782) plotted on 48-month time series from January 2006 through December 2009.

diagnosis of convulsion only (ICD-9-CM: 789.3x) when compared to patients with epilepsy (ICD-9-CM: 345.xx). Providers may have decided to stop prescribing AEDs over time in these members based on a cautious watchful-waiting and intermittent risk–benefit review [31].

Members with epilepsy and comorbid psychiatric disorder(s) may represent a more severely affected group of patients in terms of medical illness since comorbid psychiatric disorder has been reported as an independent risk factor for a decreased quality of life as well as increased mortality in patients with epilepsy [32–34]. Because of the potential to have members with more severe disease, the percentage with AED prescription claims in this diagnostic group appears to increase consistently over time (Fig. 2).

On average, the percentage of members with AED prescription claims was relatively low compared to the other two diagnostic groups for the psychiatric disorder alone diagnostic group (Fig. 2). This finding was expected because several AEDs are not FDA-approved for psychiatric conditions and are associated with off-label use [16,28,35]. Despite the potential off-label use, the percentage of members with AED prescription claims does increase over time.

This study has several strengths that must be considered. This is the first study to examine the association between the FDA AED warning and the AED prescription claims using real-world administrative data. Previously, only one study was conducted where Shneker et al. [12] surveyed neurologists to determine the impact of the FDA suicidality alert on their attitude and behavior when prescribing AEDs. The author reported a low impact of the FDA alert on clinical practice. The current study supports the Shneker et al. [12] findings by examining a large historical Medicaid administrative dataset with a rigorous analytical approach. The longitudinal feature of the administrative data strengthens the ability to determine temporal relationships between predictor and outcome variables. Finally, the use of a GEE estimation technique is a major advantage because it uses individual-level data and enables modeling the impact of the warning on AED prescription claims after accounting for individual characteristics [36]. Additionally, this technique accounts for the within subject autocorrelation by incorporating a working covariance matrix [36]. In contrast, previous studies related to other FDA risk communications have used the aggregated time-series design wherein data are collapsed across individuals to create a time series [37,38].

This study has important limitations to consider. The AED-related suicidality issue was first raised in 2004, but reliable administrative claims data were not available before January 1, 2006 in the Oklahoma Medicaid dataset. The time period included after the FDA warning was very short, potentially too short to measure a potential long-term change in outcome measures. There may be several other factors including advertising by pharmaceutical manufacturers, competing communications by professional organizations, publication of new safety and effectiveness information, and media reports that could affect the utilization pattern of AEDs during that period. These external factors could not be accounted for in this study. The design of this study did not allow for the examination of utilization patterns of specific AEDs in patients with epilepsy and/or psychiatric disorder because certain AEDs (i.e., gabapentin) are widely used off-label in diabetic neuropathy, migraine, or chronic pain [28]. These indications may not be representative in the study population and produce biased results for specific AEDs used. This study did not include members with incident diagnoses of epilepsy or psychiatric disorder in the analytical sample because of limited sample size. Exclusion of members taking polytherapy (2 or more AEDs, more severely ill group) at the AED prescription index date limits generalizability of these results to those receiving monotherapy at baseline. Missing data are always a potential problem, especially in research employing claims data. Because of missing data on individual physician specialty, all CNS health-care providers were collapsed into one category, and we could not assess the impact of the warning within CNS health-care providers. Finally, Medicaid claims data employed in this research came from a single state, which may limit generalizability of results.

5. Conclusions

The FDA suicidality warning issued in May 2009 appeared to have a small immediate impact on AED prescription claims, but no significant changes in trend were detected throughout the study period. Also, the FDA AED-related suicidality warning does not appear to have influenced AED prescription claims across diagnostic groups. Future research is required to examine the impact of the FDA suicidality warning on the utilization pattern of specific AEDs.

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Table 3
Segmented regression model: Point estimates with 99% CI, % change in log odds of AED Rx claims with 99% CI, and p-value among the study population in the Oklahoma Medicaid setting from January 2006 through December 2009.

Level/trend	Epilepsy and/or psychiatric disorder(s) (N = 9289)		Epilepsy alone (n = 345)		Epilepsy + comorbid psychiatric disorder(s) (n = 3162)		Psychiatric disorder(s) alone (n = 5782)	
	Point estimates (99% CI)	Change in log odds of AED Rx claims % (99% CI)†	Point estimates (99% CI)	Change in log odds of AED Rx claims % (99% CI)†	Point estimates (99% CI)	Change in log odds of AED Rx claims % (99% CI)†	Point estimates (99% CI)	Change in log odds of AED Rx claims % (99% CI)†
Baseline level (β_0)	0.62** (0.39 to 0.84)	Referent	1.08** (0.52 to 1.65)	Referent	0.61** (0.42 to 0.81)	Referent	−0.66** (−0.86 to −0.47)	Referent
Baseline trend (β_1)	0.01** (0.008 to 0.013)	Referent	−0.01 (−0.03 to 0.001)	Referent	0.013** (0.01 to 0.02)	Referent	0.01** (0.006 to 0.013)	Referent
Level change at FDA alert (β_2)	−0.04 (−0.07 to 0.002)	−6.5% (−11.3 to 0.3)	−0.06 (−0.26 to 0.14)	−5.5% (−24.1 to 13.0)	−0.06 (−0.13 to 0.002)	−9.8% (−21.3 to 0.3)	−0.02 (−0.07 to 0.03)	−3.0% (−10.6 to 4.5)
Trend change during FDA warning (β_3)	−0.002 (−0.007 to 0.003)	−20.0% (−70.0 to 30.0)	0.002 (−0.02 to 0.03)	20.0% (−200.0 to 300.0)	−0.005 (−0.013 to 0.003)	−38.5% (−100.0 to 23.0)	−0.0003 (−0.01 to 0.01)	−3.0% (−100.0 to 100.0)
Level change at FDA warning (β_4)	−0.09** (−0.14 to −0.05)	−14.5% (−22.6 to −8.1)	−0.09 (−0.31 to 0.13)	−8.3% (−28.7 to 12.0)	−0.09* (−0.17 to −0.01)	−14.8% (−27.9 to −1.6)	−0.1** (−0.16 to −0.04)	−15.2% (−24.2 to −6.0)
Trend change after FDA warning (β_5)	0.008 (−0.002 to 0.02)	80.0% (−20.0 to 200.0)	0.009 (−0.03 to 0.05)	90.0% (−300.0 to 500.0)	0.002 (−0.02 to 0.02)	15.4% (−153.8 to 153.8)	0.01 (−0.001 to 0.025)	100.0% (−10.0 to 250.0)

The models were estimated using PROC GENMOD (SAS 9.2) with a binomial distribution logit function. The correlation structure was AR (1). The overall model was adjusted for a number of covariates including age, sex, race, diagnostic groups, neurological comorbidities, other comorbidities, use of psychotropic therapy, physician specialty, geographical region, and MSA. All three stratified diagnosis-specific models were adjusted for a number of covariates excluding diagnostic groups.
†Example of calculating change in log odds of AED Rx claims %.
% change in trend of AED Rx claims during the FDA warning (β_3) in patients with epilepsy and/or psychiatric disorder(s) (N = 9289) = trend change during the FDA warning period / baseline trend in prewarning period = $\beta_3 * 100 / \beta_1 = 0.002 * 100 / 0.01 = 20.0\%$.
Calculation of 99% CI: (a) lower bound = $0.007 * 100 / 0.01 = 70.0\%$; (b) upper bound = $0.003 * 100 / 0.01 = 30.0\%$.
% change in log odds of AED Rx claims during the FDA warning period was −20.0% (99% CI: −70.0 to 30.0). Other calculations were performed in a similar manner. Negative sign indicates the decline in log odds of AED Rx claims and was not included in the mathematical calculation.
* $p < 0.01$.
** $p < 0.0001$.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose. No financial or material support was received by any of the authors in conducting this research or the preparation of this manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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